



NATIONAL HEMOPHILIA FOUNDATION

for all bleeding disorders

October 7, 2019

MASAC Medical Communication on Particulate Matter in Emicizumab (HEMLIBRA) and Other Biologic Agents

Background

Since the development of intravenous therapies, the presence of particulate matter in injectable drugs has been a concern for clinicians. While some particles can come from outside sources (eg. when the product is prepared for use), others are “intrinsic” to the manufacturing process specific to the drug. In the latter case, sources for these particles may be the solution itself and its ingredients, contact with components used in manufacturing (eg. tubing) or the product’s package (eg. rubber stopper). In some cases, intravenous infusion of injectables which contain particulate matter has been associated with harm. Accordingly, the United States Pharmacopeia (USP) has established fixed limits for the amount of particulate matter in preparations intended for intravenous use and states that, prior to dispensing, all containers of intravenous preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter in their contents and these are not distributed if the amount exceeds the set limit. Test procedures for determination of the presence of particulate matter are set by the USP and manufacturers are required to follow these industry standards. Particulate matter in injectables that are intended for intramuscular and subcutaneous administration would not carry the same risk as for intravenous administration, but industry standards still apply and limits are determined under review by the regulators (eg. FDA).

Context for this Medical Communication

On October 5, 2019, MASAC received the following information from representatives of Roche/Genentech, manufacturers of emicizumab (HEMLIBRA):

During a routine examination of drug product batches, as part of our quality assurance systems and processes, hardly visible, translucent particles were identified in Hemlibra® (emicizumab), outside our particle specification.

These particles are inherent to the drug product and based on toxicology and safety assessments and review of available data, the benefit/risk profile of Hemlibra remains unchanged as a result. They consist of protein (Hemlibra drug substance) and silicone oil

(PDMS, polydimethylsiloxane). Silicone oil is a non-toxic, organic polymer that is included in all parenteral medicines. Translucent particles are commonly observed and present in other approved biologics.

We have informed health authorities in March 2019. The European Medicines Agency (EMA), US Food and Drug Administration (FDA), Swissmedic, Health Canada, and the Ministry for Health, Labour and Welfare (MHLW) in Japan all agreed with our assessment that the benefit/risk profile of Hemlibra remains unchanged, and have supported the continued distribution of Hemlibra to patients to avoid therapy interruption. We have submitted the results of our final analysis to the health authorities and continue to engage with these health authorities.

We are committed to producing high quality products for our patients, which is why we have rigorous manufacturing monitoring, controls and testing in place for all our medicines, including Hemlibra.

MASAC Statement

After MASAC was informed of this issue on October 5, 2019, representatives from Roche/Genentech were available to answer questions.

The following points were presented to MASAC:

- The appearance of particulate matter includes vials of emicizumab that were used both during the clinical trial program and commercially available product. The particulate matter exceeded the manufacturers pre-established threshold.
 - a. In a look-back at all previous lots of emicizumab, this problem has been present since the initial clinical trials but was only recently identified.
- This is a manufacturing issue that is well-described in scientific literature and subject to oversight by regulatory health authorities who have provided their assessment and deemed that there is no change to the risk-benefit evaluation for use of emicizumab.
 - a. The finding of particulate matter in a limited number of vials of emicizumab has been reviewed by regulatory health authorities in the United States, Switzerland, Canada, Japan and the European Union who have all determined that there is no change to the risk-benefit evaluation of emicizumab as it is currently manufactured and available for patient use.
- Risk from particulate matter in injectables intended for subcutaneous administration is likely reduced compared to intravenous injectables.
- No adverse events linked to the particulate matter have been reported. No reports from end-users of product have been received by Roche/Genentech up to this point.

Based on the information that MASAC has available at this time, including information on the assessments of regulatory health authorities, MASAC does not recommend a change in prescribing practice nor interruption in the use of emicizumab for patients already using the product.

Further, MASAC has the following recommendations:

- MASAC expects that Roche/Genentech will conduct a full review of their manufacturing and quality control processes to determine how they may better ensure that all product meets their industry standard on the limits to particulate matter in HEMLIBRA
- MASAC has requested notification of any regulatory feedback of this manufacturing issue that changes the risk-benefit assessment and has requested any follow up on this matter after Roche/Genentech have completed their manufacturing process and quality control review
- The current recommendation regarding no change in prescribing practice and no interruption in the use of emicizumab is an interim recommendation pending our assessment of the full review by Roche/Genentech of their manufacturing and quality control

Any patient or caregiver who has questions or concerns about this matter should contact their Hemophilia Treatment Center. MASAC will continue to closely monitor this matter and provide additional updates as warranted.

References

United States Pharmacopeia. <https://www.usp.org/biologics>. Accessed October 6, 2019.

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Tran T, Kupiec TC, Trissel LA. Particulate Matter in Injections: What is It and What are the Concerns? *International Journal of Pharmaceutical Compounding* (2006) 10(3):202-204.